

Prevention of Nickel Allergy: The Case for Regulation?

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KEYWORDS

• Metal • Prevalence • Risk factors • Clinical
• Diagnosis • Treatment • Barriers

Nickel is a ubiquitous metal found in the Earth's core as well as in soil, water, and air. It was first discovered in 1751 by Swedish chemist Baron Axel Fredrik Cronstedt.¹ Nickel is used worldwide, mainly in the manufacture of steel, because of its strength and resistance to oxidation. Stainless steel is composed of iron alloyed with at least 10% chromium; other metals such as nickel and molybdenum are often added to prevent staining, rusting, and corrosion. Not only can nickel be combined with stainless steel, but it can also be combined with other transitional metals including cobalt, palladium, iron, titanium, vanadium, and magnesium. Nickel-containing metal alloys are abundant in most industrialized countries and can be found in everyday items such as jewelry, eyeglass frames, watchbands, belt buckles, snaps, and coins. Nickel allergy is the most common metal allergy and the most common overall allergen detected in patch-test populations.^{2,3}

PREVALENCE OF NICKEL ALLERGY

The North American Contact Dermatitis Group (NACDG), a group of 13 dermatologists in the United States and Canada, collects de-identified data on patch-tested patients and publishes the epidemiologic data every 2 years. Since 1992, nickel has been the most frequent positive allergen in the group's screening panel of 65 allergens.²

Supporting data show that rates of nickel sensitivity have increased over the past decade. In 1992–1995, 14.5% of patients tested had a positive patch test to nickel compared with 18.8% of patients in 2003–2004 ($P < .0001$, **Fig. 1**).⁴ Patients under age 18 had significantly higher rates of nickel sensitivity compared with older patients, and women also had significantly higher rates of nickel allergy than men.⁴

Nickel contact dermatitis is common in other industrialized countries. The European Surveillance System on Contact Allergies (ESSCA), a group of dermatologists who collect data on patch-tested patients from nine countries in Europe, reported that nickel sulfate was the most frequently positive allergen and affected 17.3% of patients tested in the years 2002–2003.³ Within the ESSCA, the highest rates of nickel allergy occurred in Italy (31.7%), where children are exposed to costume jewelry at a young age and where a nickel directive was only implemented in July 2001.³ The lowest rates of nickel sensitivity were in Denmark (8.1%), probably due to the fact the nickel has been regulated in consumer goods since 1992.^{3,5}

IMMUNOLOGY AND GENETICS OF NICKEL ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is a type IV reaction, also known as delayed type hypersensitivity. This

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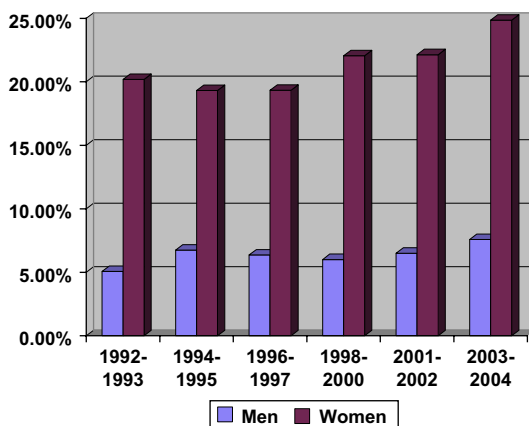


Fig. 1. Rising prevalence of positive patch tests to nickel by gender, NACDG patients. (Data from Rietschel RL, Fowler JF, Warshaw EM, et al. Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis* 2008;19:16–9.)

reaction results from skin contact with the metal ions, which bind to proteins of the skin and induce a cellular immune response. Nickel has been shown to elicit a mixed Th1- and Th2-type cytokine response in peripheral blood mononuclear cells (PBMC) from patients with known sensitivity to nickel. In vitro measurements of these responses to nickel have shown increases in expression of IL-2, IL-4, IL-13, and INF- γ from PBMC of sensitized patients.⁶ The immunologic response to nickel is similar to that in patients allergic to other metals.^{6,7}

Nickel ions act like a conventional peptide in terms of T-cell receptor activation. After nickel has come into contact with the skin, it forms an antigenic complex with a self-peptide and a specific major histocompatibility complex (MHC) molecule on Langerhans cells, which are specialized antigen-presenting cells on the skin. These Langerhans cells then migrate to the draining lymph nodes to sensitize naïve T cells.⁸ This specific nickel and MHC-peptide complex is then presented to a repertoire of T-cell receptors, eventually resulting in an inflammatory cascade. A nickel atom is at the center of the complex, forming coordinate bonds with the MHC-peptide complex and the T-cell receptor.⁹ Because the activation of the immune response requires specific peptides and MHC molecules, only sensitized individuals develop an allergic reaction to nickel. However, nickel can also activate T cells through other mechanisms that are not dependent on MHC molecules.

Genetic studies of nickel allergy have been inconclusive.^{10,11} Some animal research has shown an inherited predisposition to the development of

allergic contact dermatitis. Family studies have also shown a tendency toward higher rates of allergic contact dermatitis within related individuals, but such studies have not been able to conclusively control for environmental exposures.¹¹ In a large female twin study, there was a trend toward concordance for nickel allergy among female monozygotic twins compared with dizygotic twins, but the results were not statistically significant and may have been skewed by the fact that only twins with hand eczema were studied.^{12,13} Most experts believe that nickel allergic contact dermatitis is related to environmental exposure rather than genetic factors.¹²

RISK FACTORS FOR CONTACT ALLERGY TO NICKEL

The most important risk factors for developing nickel sensitivity are female sex and younger age. The relative risk is 3.74 in women compared with men (95% CI 3.51–3.98) and the relative risk for those 30 years or less is 3.23 (95% CI 3.03–3.45).¹⁴ However, 12.9% of children under age five (54% boys and 45% girls) were found to be nickel sensitive in a population-based study of 85 children in Denver.¹⁵ This suggests that exposure in childhood does not have the same female predominance as in adult populations. Ear piercing is also an important risk factor for nickel sensitization.¹⁶ A study of 567 Danish citizens found that nickel sensitization was higher among patients with pierced ears (14.8%) compared with those without ear piercings (1.8%).¹⁷ The higher rates of ear piercings in women compared with men is often used to explain the differences in nickel allergy between the sexes. As the popularity of body piercings increases in both sexes, the rate of nickel allergy will also likely increase.

Occupations shown to be at high risk for nickel exposure and sensitization include metal workers, retail clerks, hairdressers, domestic cleaners, and caterers. Tasks performed by metal workers include welding, nickel electroplating, operating machines with metal wires and alloys, engineering metal alloys, lining steel furnaces, metal cutting, and pattern making with metal sheets. Hairdressers handle nickel-plated scissors and other tools. Retail clerks handle metal coins and jewelry. Domestic cleaners and caterers also handle metal objects in the work environment.¹⁸

CLINICAL PRESENTATION

The most common presentation of nickel contact dermatitis is a well-demarcated, erythematous, papular eczematous plaque at the site of nickel

contact. Common locations include the face from eyeglasses, earlobes from earrings, wrist from watches, neck from necklaces, and periumbilical skin from belt buckles, buttons, or snaps (**Figs. 2 and 3**). In the acute state, blisters and weeping may be present, whereas lichenification is typical of chronic exposure. Because Langerhans and T cells circulate throughout the body, areas that are not in direct contact with the allergen can also be affected. This immune-mediated reaction is referred to as autoeczematization or an id reaction (**Fig. 4**). In a small study of 30 children, id reactions were seen in 50% of children with nickel allergic contact dermatitis.¹⁹ The study also found that children as young as age 1 can be sensitized to nickel and that a periumbilical skin eruption was the most common location for the skin rash.

Hand dermatitis due to contact with nickel-plated items such as scissors or coins is not uncommon. Vesicular hand dermatitis due to oral ingestion of nickel in food has also been described but is controversial.¹ Systemic contact dermatitis has also been described with oral ingestion of dietary nickel; the most sensitive patients may react to just 0.22–0.35 mg of daily nickel intake.²⁰ Foods high in nickel content include whole wheat, oatmeal, chocolate, beans, nuts, and dried fruit. Vitamins may even contain added nickel. Nickel can also leach from cans and stainless steel cooking utensils into foods. The nickel content of fruits and vegetables varies according to soil nickel content. Some authorities recommend a low nickel diet for patients with known nickel allergy.¹

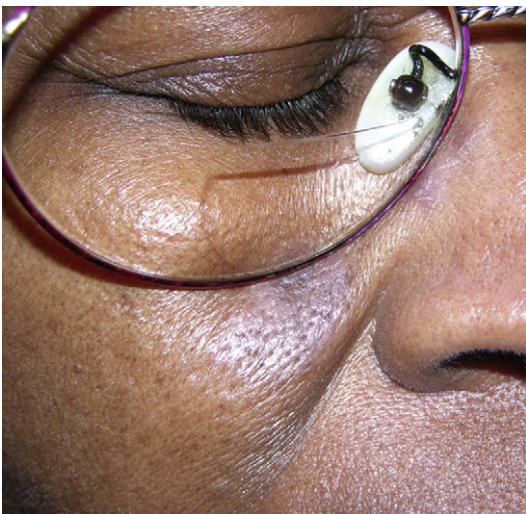


Fig. 2. Allergic contact dermatitis from nickel-containing eyeglass frames. (Courtesy of C. A. Dunnick, MD, Denver, CO.)



Fig. 3. A classic example of nickel allergic contact dermatitis in the periumbilical area. (Courtesy of C. A. Dunnick, MD, Denver, CO.)

NICKEL ALLERGY FROM IMPLANTED METAL DEVICES

Despite the fact that stainless steel is generally considered safe for nickel-sensitive patients, nickel can be released by stainless steel alloys used in medical devices in quantities sufficient to elicit allergic reactions.²¹ Furthermore, repeated contact with sweat and saliva may accelerate the release of nickel ions from these stainless steel devices. There are rare reports of orthopedic implants which have caused local and generalized eczematous reactions which have resolved with removal of the metal implant.^{22,23} There are also reports of metal-on-metal joint prosthesis failures attributed to nickel allergy, although definitive tests are lacking.²⁴ Patients may react to dental prostheses as well as orthodontic wires and braces.^{21,25} Skin staples and peripheral intravenous catheters may also cause reactions.^{26,27} Most concerning is the possibility of metal allergy



Fig. 4. The same patient as in **Fig. 3** demonstrates an autoeczematization (id) reaction. Note the uniform appearance of the flat-topped papules on the upper arm at a site remote from nickel contact. (Courtesy of C. A. Dunnick, MD, Denver, CO.)

contributing to in-stent restenosis of endovascular coronary stents.^{28,29}

Due to the fact that incidences of implant-related cutaneous allergies are rare, the epidemiology is not well established.³⁰ Observations about the relationship between implants and dermatitis have been mostly correlative and shown in case study reports. A study by Reed and colleagues³¹ showed that patch testing performed after the implants were placed had limited value, because patients did not have positive patch test results to the components of their implants. Patch testing completed before implantation, however, may provide guidance for selecting implant device materials that will not invoke a reaction. Currently it is unknown whether implants play a causal role in cutaneous metal allergies and there are no set criteria for dealing with cutaneous allergies that may be implant-related.

DIAGNOSIS AND TREATMENT

Nickel allergic contact dermatitis should be considered when dermatitis is present in locations of exposure to nickel-containing products. The standard for diagnosis of allergic contact dermatitis is patch testing. Patch testing involves placing nickel sulfate (2.5% or 5%) in petrolatum in direct contact with the skin for 48 hours and then examining the skin for a local reaction 72 to 96 hours later. Positive reactions exhibit erythema, induration, and papules (**Fig. 5**). Strong positive reactions may even result in a localized vesiculobullous reaction.

Skin biopsy is not necessary for the diagnosis of allergic contact dermatitis. Biopsy findings may support a diagnosis of allergic contact dermatitis, but are not specific as similar reaction patterns can also be seen in drug eruptions and



Fig. 5. This patient patch-tested positive to a nickel-containing coin. (Courtesy of C. A. Dunnick, MD, Denver, CO.)

eczematous dermatitis. Histology shows spongiosis, mixed dermal inflammatory infiltrate with lymphocytes, histiocytes, and eosinophils, and at times intraepidermal vesiculation and bulla.

The treatment of nickel contact dermatitis is primarily aimed at prevention of the dermatitis through allergen avoidance. However, medical treatment is indicated for symptomatic relief of allergic contact dermatitis. Various studies have shown the effectiveness of potent topical steroids such as fluticasone propionate 0.005% ointment, clobetasol butyrate 0.05% cream, and fluocinonide 0.05% ointment.^{32,33} As in the treatment of atopic dermatitis, these topical steroids can be applied twice a day until lesions are resolved, which may take 3 to 4 weeks.³⁴ Both topical steroids and calcineurin inhibitors have also been shown effective in the treatment of acute areas of allergic contact dermatitis.³⁵ Antihistamines, such as hydroxyzine or cetirizine can be useful to help control pruritus. For a severe acute reaction, such as a vesiculobullus reaction involving more than 10% of the body surface area, systemic steroids may be indicated.³⁶ Since nickel allergic contact dermatitis is immune mediated with the possibility of new lesions developing for up to 3 weeks, treatment with oral steroids should be tapered over 3 weeks. An allergic flare may result if oral steroids are prematurely discontinued.³⁷

PREVENTION

Allergen avoidance is the most effective strategy to avoid nickel contact dermatitis. Elastic can replace metal zippers and buttons in clothing. Generally, stainless steel, sterling silver, platinum, and titanium are safe in patients with nickel allergy. Yellow gold that is less than 18K and white gold may contain allergenic amounts of nickel. Patients should be educated about the availability of a nickel detection kit (dimethylglyoxime [DMG] test). The DMG test is a rapid, easy, and readily available method for detecting nickel in metal objects.³⁸ DMG on a cotton swab will turn pink if a metal object contains detectable nickel. Patients can test items in the store prior to purchase without harming the item.

Coating a nickel object with a physical barrier may prevent release of nickel ions. Jewelry can be rhodium-plated by a jeweler, but this can wear off over time. Nail polish is commonly recommended as a barrier to coat nickel objects; however, it may be ineffective as it can be washed off, scratched off, or worn away. Recently, four types of barrier coatings (two brands of clear nail polish, super glue, and Nickel Guard) were applied to nickel coins and then assessed for efficacy in

yielding negative dimethylglyoxime test results. The investigators found that a nail polish (“Beauty Secrets Hardener”) and Nickel Guard were equally effective in yielding a negative DMG test result after applying at least two coats, but Beauty Secrets Hardener was the more cost-effective choice.³⁹

If allergen avoidance in clothing is not practical or desirable, an iron-on cloth can be used. Iron-on cloths have been traditionally used to mend holes in clothing and are available in a variety of colors and designs at fabric, arts and crafts, and department stores. As a nickel barrier, it can be ironed on to the inside of the metal portion of clothing. This provides a hidden barrier, unlike sewn-on patches that can show visible stitches on the outside of garments.

Another physical barrier is duct tape. This can adhere to the inside of buttons or snaps. The advantage of duct tape is that it is economical, easy to apply, and widely available. This works well in those articles of clothing that are worn occasionally and require a barrier without much preparation or advanced notice. The disadvantage of duct tape is that the ends may become ragged and cause irritant contact dermatitis with prolonged use. The 11-year-old nickel-allergic patient in **Fig. 6** employed duct tape.

The third technique for preventing nickel allergic contact dermatitis consists of chemical barriers. Barrier creams act either by chelating the positive ionic charge and rendering the metal inactive or by preventing the penetration of nickel through the skin. Nickel chelators have been investigated for their ability to bind nickel and prevent the symptoms of nickel allergic contact dermatitis since 1951.⁴⁰ In two reports, pretreatment with disodium ethylenediamine tetra-acetate blocked the effect of nickel-induced allergic contact dermatitis

during a patch test.^{41,42} In another study of 28 nickel sensitized patients, pretreatment with 10% diethylenetriaminepentaacetic acid decreased nickel-specific patch test reaction.⁴³

With respect to nonchelating barrier creams, the rationale for their effect is that they provide protection against the invasion of foreign products, such as nickel, and against excessive transepidermal water loss. Application of a moisturizing cream (a non-ionic oil-in-water emulsion containing 9% glycerin and 4% evening primrose oil) after a nickel-mediated patch test reaction resulted in significantly better recovery of the disrupted skin with reduced transepidermal water loss in the 12 patients tested.⁴⁴ Regular use of skin moisturizers may also help prevent skin barrier damage in nickel allergic patients.⁴⁵ The absorption of nickel through the skin can also be decreased with a cream containing propylene glycol, petrolatum, and lanolin.⁴⁶ More studies are necessary to determine efficacy of chelating and nonchelating barrier creams in nickel contact dermatitis.

PRIMARY PREVENTION AND REGULATION OF NICKEL IN CONSUMER ITEMS

Because of the increasing prevalence of nickel sensitivity, several European countries have implemented regulations to limit the amount of nickel released from jewelry and other objects in close contact with the skin. The European Union Nickel Directive was adopted in 1994 and limits the amount to no more than 0.05% nickel content in posts used for body piercings. Furthermore, it limits the amount of nickel released from objects in direct and prolonged contact with the skin to no more than 0.5 μg nickel/ cm^2 /week. It also mandates that these objects, such as jewelry, watches, buttons, and zippers, shall maintain this requirement for 2 years of normal use.⁴⁷

Regulation of nickel has successfully lowered rates of nickel sensitization. In Germany, nickel allergy in women under age 30 decreased significantly from 36.7% (in 1992) to 25.8% (in 2001).⁴⁸ In Denmark, nickel sensitivity in children under age 18 fell from 24.8% to 9.2% from 1985–1986 to 1997–1998.⁴⁹ Danish schoolgirls whose ears were pierced prior to nickel regulation in 1992 had an odds ratio of 3.34 for nickel sensitization in contrast to girls whose ears were pierced after regulation (OR 1.2).⁵ In the same study, 250 items of jewelry were tested with DMG and none released nickel, indicating successful compliance by jewelry manufacturers. Another study in Sweden documented that in 1999, 25% of 725 items tested positive for released nickel whereas only 8% of 786 items tested



Fig. 6. The 11-year-old nickel-allergic patient here employed duct tape as a physical barrier for the nickel containing button at the waistline of these pants. (Courtesy of C. A. Dunnick, MD, Denver, CO.)

positive for nickel in 2002–2003 after nickel regulation was introduced.⁵⁰

To raise awareness about nickel allergy, the American Contact Dermatitis Society named nickel the 2008 Contact Allergen of the Year⁵¹ and has sponsored resolutions recommending limits in consumer products similar to those adopted in Europe. The American Academy of Dermatology is considering this resolution for adoption as part of its platform.

SUMMARY

Nickel is the most common allergen detected in patch-tested patients, affecting up to 35.8% of young females in this group. Management of nickel allergy consists of avoidance and barrier methods. Successful primary prevention will likely require governmental regulation of nickel content in consumer items.

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